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Kinetic Resolution of Diols and Pyridyl Alcohols by Cu(II)(borabox)-Catalyzed Acylation

Clément Mazet, Stephen Roseblade, Valentin Köhler, and Andreas Pfaltz*

Department of Chemistry, University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

andreas.pfaltz@unibas.ch

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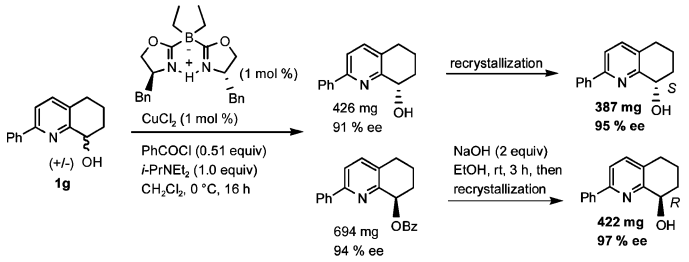
ABSTRACT



Boron-bridged bisoxazoline (borabox) ligands have been used in the copper(II)-catalyzed benzoylation of pyridyl alcohols and 1,2-diols. Efficient kinetic resolution of 1,2-diols was achieved using both borabox and bisoxazoline (box) ligands. Borabox ligands induced high selectivities in the benzoylation of suitable pyridyl alcohols, where they outperformed bisoxazolines. In addition, highly enantioselective Cu(II)(borabox)-catalyzed benzoylation has been used for the synthesis of both enantiomers of a pyridyl alcohol.

The design of C_2-symmetric nitrogen-based chiral ligands for asymmetric catalysis has developed rapidly since the semicorrin ligands **1** were introduced (Figure 1).[1] The bisoxazolines **2** have emerged as especially versatile ligands for achieving high levels of stereocontrol in various metal-catalyzed asymmetric reactions.[2] In this context, we recently introduced a new class of monoanionic bisoxazolines **3** (borabox) in which the central bridging carbon atom has been replaced by a quaternary boron atom. These ligands were found to induce high enantioselectivities in the copper-catalyzed asymmetric cyclopropanation of olefins and in the asymmetric desymmetrization of *meso*-1,2-diols, where they outperformed the bisoxazolines **2**.[3]

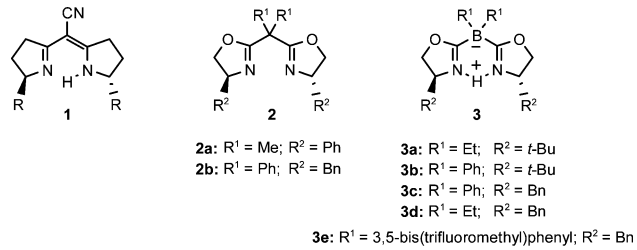


Figure 1. Semicorrin, bisoxazoline (box), and borabox ligands.

Kinetic resolution of alcohols by asymmetric acylation with nonenzymatic reagents or catalysts has attracted attention recently.[4] For instance, Matsumura and co-workers reported that monobenzoylation of *trans*-1,2-diols using 5 mol % of $CuCl_2$ and box ligand **2a** was highly selective.[5]

Herein, we report kinetic resolution of 1,2-diols and pyridyl alcohols by Cu(II)(borabox)-catalyzed acylation.

(1) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem.* **1986**, *98*, 1028−1029; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1005−1006. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339−345.

(2) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2232. (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151−4202. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(3) Mazet, C.; Köhler, V.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4888−4891; *Angew. Chem.* **2005**, *117*, 4966−4969.

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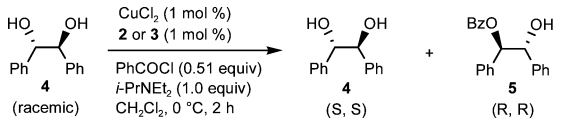
Initial studies of the Cu(II)-catalyzed benzoylation of 1,2-diphenylethane-1,2-diol **4** using benzoyl chloride and *i*-PrNEt$_2$ with ligand **3d** established that decreasing the catalyst loading from 5 to 1 mol % did not cause a significant decrease in the selectivity factor *S* or the conversion.[6]

Subsequent ligand screening using catalyst loadings of 1 mol % revealed that borabox ligands possessing benzyl substituents at the stereogenic center of the oxazoline unit gave higher selectivities than those bearing *t*-Bu substituents. Ligand **3e**, incorporating electron-poor perfluorinated aryl groups at the boron atom, gave an *S* value of 225 under optimized conditions. Bisoxazolines **2a** and **2b** were also found to be highly selective, giving *S* values of around 200 (Table 1).[7]

Table 1. Kinetic Resolution of 1,2-Diphenylethane-1,2-diol

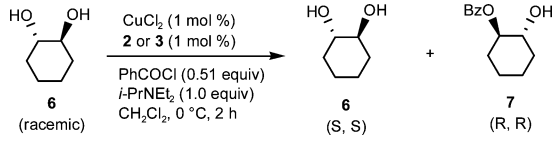


entry	ligand	ee **4** (%)[a]	ee **5** (%)[a]	conversion(%)[b]	S^b
1	**2a**	95	96	50	182
2	**2b**	96	95	50	217
3	**3a**	14	39	27	3
4	**3b**	38	45	46	4
5	**3c**	80	86	48	32
6	**3d**	82	93	47	71
7	**3e**	98	96	51	225

[a] HPLC assay. [b] Ref 7.

By comparison, benzoylations of *trans*-1,2-cyclohexanediol **6** were less selective giving *S* values ranging from 16 to 21. For this substrate, borabox ligands **3d** and **3e** were found to induce slightly higher selectivities than box ligand **2a** (Table 2).

Table 2. Kinetic Resolution of 1,2-Cyclohexanediol

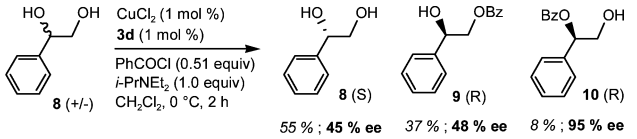


entry	ligand	ee **6** (%)[a]	ee **7** (%)[a]	conversion (%)[b]	S^b
1	**2a**	17	86	17	16
2	**3d**	74	79	48	19
3	**3e**	64	83	44	21

[a] HPLC assay. [b] Ref 7.

The resolution of racemic 1,2-phenylethanediol **8** was also investigated. Benzoylation occurs preferentially at the primary alcohol giving rise to monobenzoylated products **9** and **10**, along with the enantioenriched starting diol **8** (Scheme 1).[8]

Scheme 1. Kinetic Resolution of 1,2-Phenylethanediol



The ee values of the enantioenriched diol **8** and the monobenzoylated secondary alcohol **9** were moderate with all ligands tested.[9] Although the overall process is rather inefficient, the higher ee value observed for the primary alcohol **10** is consistent with the selectivities obtained in the benzoylation of 1,2-diphenylethane-1,2-diol and 1,2-cyclohexanediol. These results indicate that the presence of a large substituent adjacent to the hydroxy group is required for high selectivity.

Chiral pyridyl alcohols are valuable intermediates in the synthesis of ligands for asymmetric catalysis, chiral nucleophilic catalysts, and biologically active compounds.[10] Approaches to their asymmetric synthesis have focused on enantioselective reduction of the corresponding ketones.[11] Kinetic resolution of pyridyl alcohols is an attractive alternative, and an enzymatic approach has been reported.[12] We

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(5) (a) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052−2053. For the use of a chiral tin catalyst, see: (b) Iwasaki, F.; Maki, T.; Nakashima, W.; Onomura, O.; Matsumura, Y. *Org. Lett.* **1999**, *1*, 969−972. (c) Iwasaki, F.; Maki, T.; Onomura, O.; Nakashima, W.; Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996−1002. (d) Matsumura, Y.; Maki, T.; Tsurumaki, K.; Onomura, O. *Tetrahedron Lett.* **2004**, *45*, 9131−9134. (e) For the use of aza-bisoxazoline ligands, see: Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325−2328.

(6) See Supporting Information for details. Benzoyl chloride was found to be the best choice of acylating agent when compared to alkyl acid chlorides such as AcCl and ^{t}BuCOCl.

(7) Conversions and enantioselectivities were determined using ee values obtained from chiral HPLC of the products (pr) and starting materials (sm); conversion (C) = ee$_{sm}$/(ee$_{sm}$ + ee$_{pr}$). S = ln[1 − C(1 + ee$_{pr}$)]/ln[1 − C(1 − ee$_{pr}$)] = ln[(1 − C)(1 − ee$_{sm}$)]/ln[(1 − C)(1 + ee$_{sm}$)]. See: (a) Kagan, H. B.; Fiaud, J.-C. *Top. Stereochem.* **1988**, *18*, 249−330. (b) Sih, C. J.; Wu, S. H. *Top. Stereochem.* **1989**, *19*, 63. (c) Kagan, H. *Tetrahedron* **2001**, *57*, 2449−2468. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. The selectivity factors reported here differ from those reported previously by Matsumura and co-workers. In that study, selectivity factors were determined from the enantiomeric excess of the monobenzoylated products and their isolated yields. It has been noticed in kinetic resolution using chemical or biochemical methods that this approach gives variable accuracy, leaving the major error on conversion *C*.

(8) (a) Guetté, J.-P.; Horeau, A. *Bull. Soc. Chim. Fr.* **1967**, 1747−1752. (b) Kagan, H. B. *Croat. Chem. Acta* **1996**, *69*, 669−680.

(9) See Supporting Information for details.

(10) (a) Drury, W. J., III; Zimmerman, N.; Keenan, M.; Hayashi, M.; Kaiser, S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70−74. (b) Kaiser, S. Ph.D. Dissertation, University of Basel, 2005. (c) Kang, J.; Kim, H. Y.; Kim, J. P. *Tetrahedron: Asymmetry* **1999**, *10*, 2523−2533. (d) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810. (e) Roszkowski, A. P.; Govier, W. M. *Pharmacologist* **1959**, *1*, 60. (f) Barouh, V.; Dall, H.; Patel, D.; Hite, G. *J. Med. Chem.* **1971**, *14*, 834.

became interested in this transformation in connection with our work on asymmetric hydrogenation, as cationic iridium complexes containing chiral P,N-ligands, which are derived from pyridyl alcohols, are highly selective catalysts for asymmetric hydrogenation of unfunctionalized olefins (Figure 2).[13]

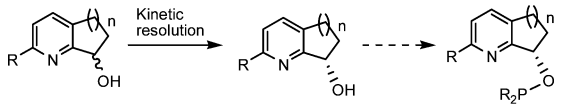


Figure 2. Pyridyl alcohol resolution during ligand synthesis.

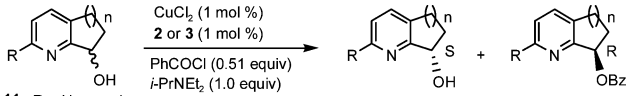
Like the diol substrates, pyridyl alcohols should be able to chelate copper(II), which is thought to be an essential requirement for achieving high enantioselectivities.[5a] To test their suitability in this process, several pyridyl alcohols were synthesized and examined in the Cu-catalyzed benzoylation. Initially, reactions were carried out using 0.5 mmol of substrate and 1 mol % of copper complex in dichloromethane at 0 °C.

We found that while the copper box complex **2b** exhibited poor selectivities with all substrates examined the selectivities obtained with the borabox ligands were generally higher, although highly dependent on the structure of the substrate (Table 3). A comparison of pyridyl alcohols **11** and **12** shows that substitution at the α-CH of the pyridine ring with a phenyl group greatly enhances the selectivity. During benzoylation of pyridyl alcohol **12**, the borabox ligands **3d** and **3e** both impart levels of enantioselectivity which are useful synthetically, with an *S* value of 51 for ligand **3e**.

Substrate **13** is benzoylated with an *S* value of 19 using ligand **3e**, indicating that when a six-membered ring is fused to the pyridine ring the enantioselectivity can be higher than that with a five-membered ring analogue. During benzoylation of substrate **14**, containing a phenyl group α to the pyridine N atom and a six-membered ring, borabox ligands **3d** and **3e** were highly enantioselective, giving *S* values of around 100. Substrate **15**, containing an α-chloro substituent, exhibited selectivities similar to those for the unsubstituted analogue **13**.

Kinetic resolution of 1 g of pyridyl alcohol **14** was then carried out using the readily available borabox ligand **3d** (Scheme 2).

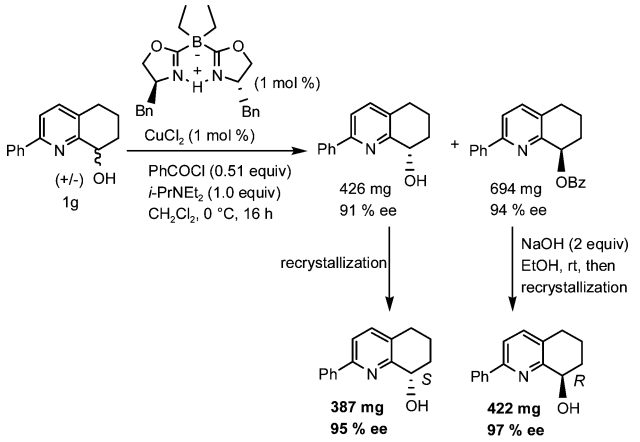
Table 3. Kinetic Resolution of Pyridyl Alcohols



substrate	ligand	alcohol ee (%)[a]	benzoate ee (%)[a]	conversion[b] (%)	S^b
11	**2b**	1	1	50	1
11	**3d**	16	33	33	2
11	**3e**	5	5	46	1
12	**2b**	8	26	24	2
12	**3d**	50	84	36	18
12	**3e**	76	91	45	51
13	**2b**	3	8	27	1
13	**3d**	>99	60	62	9
13	**3e**	83	76	52	19
14	**2b**	3	17	15	2
14	**3d**	61	96	39	92
14	**3e**	70	97	42	125
15	**2b**	6	6	53	1
15	**3d**	62	80	44	17
15	**3e**	58	65	47	8

[a] HPLC assay. [b] Ref 7.

Scheme 2. Preparative Scale Pyridyl Alcohol Resolution



Following benzoylation under optimized conditions (1 M, CH_2Cl_2, 1 mol %, 0 °C), the alcohol and benzoate were separated by column chromatography. The alcohol was recovered with an ee of 91% (*S*), and subsequent recrystallization from hexane/EtOAc provided (*S*)-alcohol in 39% yield and 95% ee. The benzoate was isolated with 94% ee (*R*); subsequent hydrolysis was accomplished without racemization to yield the (*R*)-alcohol in 42% yield and 97% ee after recrystallization from hexane/EtOAc. A straightforward synthesis of both enantiomers of the ligand precursor **14** has thus been accomplished, with the borabox ligand inducing very high enantioselectivity.

In conclusion, we have developed a catalytic system for the kinetic resolution of 1,2-diols and pyridyl alcohols which

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(12) (a) Uenishi, J.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481−2487. (b) Uenishi, J.; Hamada, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2999−3006. (c) Uenishi, J.; Hamada, M. *Synthesis* **2002**, *5*, 625−630.

(13) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642−644.

operates efficiently at 1 mol % catalyst loading. Enantioselectivities in the benzoylation of 1,2-diols are higher when a large substituent is adjacent to the hydroxy group, and excellent enantioselectivities were achieved using borabox and box ligands. We found that borabox ligands induce high selectivities during benzoylation of suitable pyridyl alcohols, where they outperformed an analogous bisoxazoline.

Acknowledgment. Financial support from the Swiss National Science Foundation is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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